370. Lung, heart, muscles and brain: the pathway of oxygen during exercise in health and COPD

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Lung structure and function in a rat model of emphysema: A longitudinal study

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Our aim was to evaluate the long term structure-function relations in a rat model of emphysema. Rats were treated with porcine pancreatic elastase (50 UI, PPE, n=21) or saline (controls, C, n=19) intratracheally. Before the treatment (day 0) and 3, 10, 21 and 105 days thereafter, respiratory impedance was measured with forced oscillation technique and tissue elastance (H) was calculated. At 3, 21 and 105 day the lungs were fixed, sections were obtained and stained with hematoxylin and eosin, modified Movat's, Masson's and Alcian blue method to visualize elastin, collagen and proteoglycans. Randomly selected regions were photographed. The images were automatically segmented and the equivalent diameter of alveolar airspaces (D), mean elastin (Me), mean collagen content (Mc) and mean proteoglycan ratio (Mp) were measured. H decreased through the time-course in the treated animals ($p<0.001$). D was different between the control and the treated groups at 21 ($p=0.027$) and 105 days ($p=0.004$). Me increased in the treated groups (21 d, 105 d: $p<0.001$), Mc decreased in the treated groups (3 d, 21 d: $p<0.001$) and Mp was different between the 2 groups (21 d: $p<0.001$, 105 d: $p=0.016$). Multiple linear regression revealed significant correlations between H, D and Me/Mc/Mp ($r^2=0.7$, $p<0.001$; $r^2=0.712$, $p<0.001$; $r^2=0.547$, $p=0.042$). We conclude that the progression of emphysema in the PPE model occurs by gradual septal wall failures leading to enlarged airspaces, which in turn decreases the tissue elastance of the lung. This irreversible process results in strong functional and microstructural relations with the components of the extracellular matrix.

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Cerebral cortex blood flow, oxygen delivery and oxygenation during normoxic and hypoxic exercise in healthy humans

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Background: During maximal hypoxic exercise a reduction in cerebral oxygen delivery may constitute a signal to terminate exercise.
Aim: To investigate whether the rate of increase in cerebral cortex oxygen delivery is limited in hypoxic compared to normoxic exercise.
Methods: We assessed frontal cerebral cortex blood flow using near infrared spectroscopy and the light-absorbing tracer indocyanine green dye, as well as frontal cortex oxygen saturation (StO_2%) in 11 cyclists during incremental exercise to the limit of tolerance (WR_{max}) in normoxia and acute hypoxia (F_IO_2:0.12).
Results: In normoxia, cerebral cortex blood flow and oxygen delivery increased ($p<0.05$) from baseline to sub-maximal exercise reaching peak values at near-maximal exercise (80%WR_{max}: 287±9W; 81±23% and 75±22% increase relative to baseline, respectively), both leveling off thereafter up to WR_{max} (382±10W). Cerebral cortex StO_2% did not change from baseline (66±3%) throughout graded exercise. During hypoxic exercise, cerebral cortex blood flow increased from baseline to sub-maximal exercise peaking at 80%WR_{max} (213±6W; 60±15% relative increase) before declining towards baseline at WR_{max} (289±5W). Despite this, cerebral cortex oxygen delivery remained unchanged from baseline throughout graded exercise, being at WR_{max} lower than at comparable loads (287±9W) in normoxia (by 58±12%). Cerebral cortex StO_2% fell from baseline (58±2%) on moderate exercise in parallel with arterial oxygen saturation, but then remained unchanged to exhaustion (47±1%).
Conclusion: Cerebral cortex oxygen delivery is limited in hypoxia compared to normoxia, thus potentialy compromising maximal exercise capacity in hypoxia.

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Cerebral cortex oxygen delivery and exercise limitation in patients with COPD

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Background: During hypoxic exercise in healthy humans, limited frontal cerebral cortex oxygen delivery may signal the brain to cease exercise.
Aim: Whether in patients with COPD experiencing exercise-induced arterial O_2 desaturation, frontal cerebral cortex oxygen delivery is reduced, remains unknown.
Methods: By near infrared spectroscopy, we measured both frontal cerebral cortex blood flow (CBF) using indocyanine green dye, and cerebrovascular O_2 saturation ($\%StO_2$) in 12 COPD patients during constant-load exercise at 75% of peak capacity. Subjects exercised breathing air, 100% O_2 or normoxic heliox, the latter two in balanced order.
Results: Time to exhaustion breathing air was less than for oxygen or heliox (394±35 vs. 670±43 and 637±46 sec, respectively). In each condition, CBF increased from rest to exhaustion. At exhaustion, CBF was higher breathing air and heliox than oxygen (30.9±2.3 and 31.3±3.5 vs. 26.6±3.2 $ml \cdot min^{-1} \cdot 100g^{-1}$, respectively), compensating lower arterial O_2 content (CaO_2) in air and heliox, and leading to similar frontal cerebral cortex oxygen delivery (air: 5.3±0.4, O_2: 5.5±0.6 and heliox: 5.6±1.0 $ml \cdot O_2 \cdot min^{-1} \cdot 100g^{-1}$). In contrast, end-exercise $\%StO_2$ was greater breathing oxygen compared to air or heliox (67±4 vs. 57±3 and 53±3%, respectively), reflecting CaO_2 rather than frontal cerebral cortex oxygen delivery.
Conclusion: Prolonged time to exhaustion by oxygen and heliox despite similar cerebral cortex oxygen delivery as in air, lower $\%StO_2$ with heliox than oxygen, yet similar endurance time, and similar $\%StO_2$ on air and heliox despite greater endurance with heliox, do not support the hypothesis that cortical oxygen delivery is important in limiting exercise capacity in COPD.

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Tissue oxygenation profiles during prolonged exercise in hypoxia

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Introduction: Tissue oxygenation is altered during hypoxia (H) at rest and during exercise(1). It remains however debated whether these perturbations are similar between tissues as well as between cerebral areas implicated in motor output. The purpose of our study was to assess the effect of hypoxic exposure on quadriceps, prefrontal (PFC) and motor cortices oxygenation during prolonged submaximal cycling in H.
Methods: After a 4-h wash-in period, either in normoxia or H, 12 subjects performed a 80-min cycling exercise at 45% of their maximal aerobic power (N_E FiO_2=21%, H_E FiO_2=11%). A 3rd condition (H_R FiO_2~9%) consisted in a 80-min resting period in which the arterial saturation (SpO_2) reached during H_E was matched by adjusting FiO_2. Oxy[HbO_2]- deoxy[HHb]- and total[THb]-haemoglobin changes were measured on each site by near-infrared spectroscopy.
Results: H_R and H_E resulted in similar SpO_2 reduction (~ -20%). Quadriceps exercise-induced [HbO_2] reductions were associated with increased and unchanged [THb] in N_E and H_E respectively, while [THb] dropped significantly in H_R. PFC showed a large [THb] increase at exercise with a four-fold [HbO_2] increase in N_E compared to H_E. Motor cortex showed similar [HbO_2] changes than PFC in H_R but not at exercise. Indeed, motor cortex [THb] was stable in H_E and N_E while [HbO_2] decreased and [HHb] increased in N_E, these latter changes being significantly accentuated in H_E.
Discussion: This study quantifies for the first time the respective effects of prolonged cycling exercise and SpO_2 drop on muscle and cerebral oxygenation responses in H and demonstrates important specificities between tissues and cortical sites.
References:
[1] Verges et al., in press, Am J Physiol.

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Exercise testing confirms the role of impaired central circulatory function and elevated right ventricular stroke work index in patients undergoing lung transplantation

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Introduction: Right ventricular (RV) workload assessed by RV Stroke Work Index (RVSWI) is a negative predictor of outcome in acute respiratory failure. Cardiopulmonary exercise testing (CPET) may have a role in detecting central circulatory impairment (CCI) in patients before lung transplantation (LTx) at risk for impaired RV function.
Aims and objectives: To demonstrate correlation of ventilatory inefficiency (VI) on CPET for detection of CCI in patients before LTx with RVSWI.
Methods: 172 patients undergoing evaluation for LTx who had CPET and right heart catheterization were included. RVSWI (stroke volume index*(mean pulmonary arterial pressure - mean right atrial pressure)*0.0136) was calculated from invasive hemodynamic data. Pearson's correlation, significance 0.05, was assessed between RVSWI and CPET parameters.
Results: RVSWI correlates highly with VI and inversely with hemodynamics on CPET, but not with peak capacity or workload.

Correlation of RVSWI and CPET parameters

	RVSWI Pearson Correlation	Significance
Peak VE (L)	0.241	0.003*
Peak SBP (mmHg)	–0.273	0.001*
Peak DBP (mmHg)	–0.178	0.033*
Peak PetCO2 (mmHg)	–0.263	0.009*
Resting PetCO2 (mmHg)	–0.216	0.009*
Peak VE/VCO2	0.204	0.013*
Peak VO2 (L/min)	0.124	0.136
Peak Watts	0.069	0.415

*p<0.05; VE, Minute Ventilation; SBP, systolic blood pressure; DBP, diastolic blood pressure; PetCO2, Pressure of end tidal CO2; VCO2, Rate of carbon dioxide produced; VO2, volume of oxygen consumed.

Conclusions: High right ventricular workload correlates with ventilatory inefficiency and impaired hemodynamics on CPET. Thus, exercise parameters may predict right ventricular work and LTx outcomes.

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Additive effects of non-invasive ventilation to hyperoxia on pre-frontal cerebral oxygenation during exercise in patients with COPD

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Rationale: Changes (Δ) in cerebral oxygenation (COx) during exercise are modulated by the dynamic coupling between O_2 delivery (cerebral blood flow and arterial O_2 content) and O_2 utilization. Non-invasive positive pressure ventilation (NIV) *per se* may improve the central haemodynamic responses to exercise thereby enhancing COx in patients with chronic obstructive pulmonary disease (COPD).
Objective: To investigate the effects of NIV (inspiratory pressure= 16 cmH_2O and end-expiratory pressure= 5 cmH_2O) *plus* hyperoxia (HiOx, FIO_2= 0.4) *versus* HiOx alone on COx during ramp-incremental exercise in patients with moderate-to-severe COPD.
Methods: Thirteen non-hypercapnic males (FEV_1=48.8±15.1% predicted) were randomly assigned to receive each intervention on different days. ΔCOx was determined by near infrared spectroscopy (fold-changes in HbO_2), oxyhemoglobin saturation by pulse oximetry (SpO_2), and cardiac output (Q_T) by impedance cardiography.
Results: As expected, SpO_2 remained near 100% throughout the tests ($p>0.05$). Area under ΔCOx on HiOx was significantly correlated with ΔQ_T (r=0.82). Peak exercise capacity did not differ between interventions (74±20 W *vs*. 78±19 W; $p<0.05$). NIV-HiOx was associated with larger increases in ΔCOx at sub-maximal levels of exercise compared to HiOx ($p<0.05$). Iso-work rate Q_T was larger with NIV-HiOx than HiOx (2.0±0.5 *vs* 1.6±0.6 fold-changes, $p<0.05$) and related to improved stroke volume ($p<0.05$).
Conclusions: NIV adds benefit to HiOx in increasing pre-frontal cerebral oxygenation in patients with COPD, an effect associated with enhanced central haemodynamic responses to exercise.

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Central hemodynamics, pleural pressure and normoxic heliox during exercise in patients with chronic obstructive pulmonary disease

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Background: Altered pulmonary mechanics, due to airway obstruction, are thought to hamper cardiac function during exercise in patients with COPD. If so, improving airflow would lead to an enhanced cardiac function.
Methods: Pleural pressure, dynamic hyperinflation and central hemodynamics, by right heart catheterisation, were simultaneously measured in patients with moderate to very severe COPD at rest and during exercise; both in ambient air and while breathing a normoxic helium-oxygen mixture (heliox).
Results: Seventeen patients were included (FEV_1: 53±17%, FEV_1/VC: 42±10%).

Breathing heliox lowered expiratory pleural pressure at rest (3.8±2.6 to 1.8±2.3 mmHg) and during exercise (8.2±3.6 to 6.1±3.3 mmHg), both $p<0.05$. During exercise we did not find any improvements in stroke volume or cardiac output. At rest we found improvements in cardiac output (6.1±1.4 to 6.6±1.1 L/min/m^2), stroke volume (80±22 to 87±19 ml/m^2) and mixed venous oxygen saturation (66±6 to 69±6%; all $p<0.05$). Dynamic hyperinflation did not improve with heliox.
Conclusion: Heliox breathing did not affect cardiac function during exercise. This implies that altered pulmonary mechanics do not substantially affect cardiac function during exercise in COPD.

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Evaluation of mechanisms determining endothelial function in patients with COPD
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Background: COPD is associated with increased cardiovascular mortality. Factors contributing to vascular damage in patients with COPD are mostly unknown. However, it has been suggested that airflow limitation, systemic inflammation, oxidative stress, sympathetic activation, hypoxia and impaired physical activity may lead to endothelial dysfunction and underpin this association.
Objective: To determine the impact of airflow obstruction, systemic inflammation, oxidative stress, sympathetic activation, hypoxia and physical activity on endothelial function in COPD.
Methods: In patients with stable COPD (GOLD stage I-IV) assessments of endothelial function by flow-mediated dilatation (FMD), conventional cardiovascular risk factors (Pocock-score), airflow obstruction (FEV1), systemic inflammation (CRP), oxidative stress (malondialdehyde), sympathetic activation (baroreflex-sensitivity), hypoxia (blood gases) and physical activity (steps per day) were performed. Associations between endothelial function and these potential underlying mechanisms were assessed in univariate and multivariate analysis.
Results: 106 patients (35% GOLD stage I/II, 25% III, 40% IV) were included. In univariate analysis FMD correlated with FEV1 ($r=0.53$, $p<0.001$), baroreflex-sensitivity ($r=0.25$, $p=0.01$), and steps per day ($r=0.27$, $p=0.01$) but not with CRP, malondialdehyde, hypoxia or Pocock-score. In multivariate analysis including all proposed mechanisms only FEV1 and steps per day were independently associated with FMD.
Conclusions: Endothelial function in COPD seems to be primarily determined by the severity of airflow obstruction and the level of physical activity.